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(54) Title: METHOD FOR TREATING CANCER USING CAMPTOTHECIN DERIVATIVES AND 5–FLUOROURACIL

(57) Abstract

A method of treating cancer, said method comprising administering to a patient in need of said treatment at least one camptothecin derivative and 5–FU in an amount and in a schedule of administration synergistically effective to treat said cancer.

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# METHOD FOR TREATING CANCER USING CAMPTOTHECIN DERIVATIVES AND 5-FLUOROURACIL

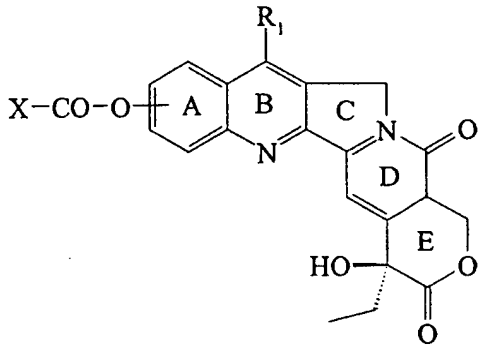
The invention relates to the treatment of cancer, preferably colorectal cancer with associations of at least one camptothecin derivative and at least one other colorectal anticancer drug and the use of such associations for an improved treatment.

More specifically the invention relates to anticancer treatments using associations of irinotecan (CPT-11 ; Campto®) and 5-FU (5-fluorouracil).

Colorectal cancer is a leading cause of morbidity and mortality with about 300 000 new cases and 200 000 deaths in Europe and the USA each year [Boyle P., Some recent developments in the epidemiology of colorectal cancer In : Bleiberg H., Rougier P., Wilke H.J., eds ; Management of colorectal cancer ; London : Martin Dunitz : 19-34 (1998) and Midgley R.S., Kerr D.J., Systemic adjuvant chemotherapy for colorectal cancer In : Bleiberg H., Rougier P., Wilke H.J., eds. ; Management of colorectal cancer ; London : Martin Dunitz, 126-137 (1998)].

Although about fifty percent of patients are cured by surgery alone, the other half will eventually die due to metastatic disease, which includes approximately 25% of patients who have evidence of metastases at time of diagnosis.

European patent EP 137,145, the disclosure of which is incorporated herein by reference, describes camptothecine derivatives of the formula:




in which, in particular, $R_1$ is hydrogen, halogen or alkyl, X is a chlorine atom or $NR_2R_3$ in which $R_2$ and $R_3$, which may be identical or different, may represent a hydrogen atom, an optionally substituted alkyl radical, a carbocycle or a heterocycle which are

optionally substituted, or alkyl radicals (optionally substituted) forming, with the nitrogen atom to which they are attached, a heterocycle optionally containing another heteroatom chosen from O, S and/or $NR_4$, $R_4$ being a hydrogen atom or an alkyl radical and in which the group X-CO-O- is located in position 9, 10 or 11 on ring A. These camptothecine derivatives are anticancer agents which inhibit topoisomerase I, among which irinotecan, for which X-CO-O- is [4-(1-piperidino)-1-piperidino]carbonyloxy, is an active principle which is particularly effective on solid tumours and in particular colorectal cancer.

The European patent application EP 74,256, the disclosure of which is incorporated herein by reference, also describes other camptothecine derivatives which are mentioned as anticancer agents, in particular derivatives of structure analogous to the structure given above and in which X-CO-O- is replaced with a radical -X'R' for which X' is O or S and R' is a hydrogen atom or an alkyl or acyl radical.

Other camptothecine derivatives have also been described, for example, in the patents or patent applications EP 56,692, EP 88,642, EP 296,612, EP 321,122, EP 325,247, EP 540,099, EP 737,686, WO 90/03169, WO 96/37496, WO 96/38146, WO 96/38449, WO 97/00876, US 7,104,894, JP 57 116,015, JP 57 116,074, JP 59 005,188, JP 60 019,790, JP 01 249,777, JP 01 246,287 and JP 91 012,070 or in Canc. Res., 38 (1997) Abst. 1526 or 95 (San Diego - 12-16 April), Canc. Res., 55(3), 603-609 (1995) or AFMC Int. Med. Chem. Symp. (1997) Abst. PB-55 (Seoul - 27 July-1 August), the disclosure of each of these is incorporated herein by reference.

Camptothecine derivatives are usually administered by injection, more particularly intravenously in the form of a sterile solution or an emulsion. Camptothecine derivatives can also be administered orally, in the form of solid or liquid compositions containing the art recognized adjuvants and/or excipients.

5-FU has been the mainstay of chemotherapy for colorectal cancer for 4 decades. It has been shown to improve both survival time (5 versus 11 months) and quality of life of patients with metastatic disease, when compared to no antitumour therapy [J. Clin. Oncol., 10(6), 904-11 (1992) and Br. Med. J., 306, 752-55 (1993)].

Insights into 5-FU molecular pharmacology have led to several strategies to modulate its cytotoxic effects. The most successful of which has been the coadministration with folinic acid (FA), which increases the degree of inhibition of thymidylate synthase [G.J.

Peters, C.L. van der Wilt, C.J. van Groeningen *et al* ; Thymidylate synthase inhibition after administration of fluorouracil with or without Leucovorin in colon cancer patients : implications for treatment with fluorouracil ; J. Clin Oncol, 12, n° 10 : 2035-2042 (1994)], depletes cellular thymidine, and induces apoptosis [C. Benz and E. Cadman ; Modulation of 5-fluorouracil metabolism and cytotoxicity by antimetabolite pretreatment in human colorectal adenocarcinoma HCT-8 ; Cancer Res, 41, 994-999, (1981)]. Folinic acid has been approved in numerous European countries for the treatment of colorectal cancer. Among the various modulations and schedules of administration, high dose infusional regimens of 5-FU plus folinic acid (5-FU/FA) are widely used in Europe and have resulted in the highest response rates (up to 44 %) and longest time to progression (around 7 months) and median survival (up to 16.6 months) over administration of bolus 5-FU/FA (J. Clin. Oncol, 15 (2), 808-815 (1997) ; J. Clin. Oncol, 16(2), 418-426 (1998) ; Ann of Oncol, 9, 727-731 (1998) ; Onkologie, 21, 403-307 (1988).

CPT-11 is one of the most active new agents in colorectal cancer. In patients resistant to 5-FU, single agent CPT-11 tested in two large phase III randomised trials resulted in a longer survival and a better quality of life compared with supportive care only [D. Cunningham, S. Pyrhönen, RD. James *et al*, The Lancet, 352, n° 9138, 1413-1418 (1998)] and also in a longer survival without deterioration in quality of life compared with 5-FU/FA best infusional regimens [P. Rougier, E. van Cutsem *et al* ; The Lancet, 352, n° 9138, 1407-1418 (1998)]. CPT-11 has thus been identified as the reference treatment in metastatic colorectal cancer (MCRC) after failure with prior 5-FU.

CPT-11 has also been shown to be at least as active as the so-called standard 5-FU/FA bolus in chemotherapy naive patients with MCRC [Proc. Am. Soc. Clin. Oncol., vol 13 (1994), (Abstr. # 573) ; J. Clin Oncol, 14(3), 709-715 (1996) ; J. Clin Oncol, 15(1) 251-260 (1997)].

Combinations of irinotecan (CPT-11) and 5-FU have already been studied in phase I studies in Japan, indicating in preliminary results that concurrent administration is feasible in terms of safety [L. Saltz et al., Eur. J. Cancer 32A, suppl 3 : S24-31 (1996)], but at the present time it has never been reported that specific administered doses combined with specific schedule of administration can lead to a significant increase of efficacy in the expected clinical responses.

A study relating to CPT-11 published by D. Cunningham, Eur. J. Cancer, 32A suppl. 3 : S1-8 (1996) suggests that CPT-11 offers a different cytotoxic approach that may complement the use of 5-FU/folinic acid in colorectal cancer in the future.

It has now been found that the administration of camptothecin derivatives combined with 5-FU/FA (folinic acid) in the following doses and using the following schedules of treatment (« AIO treatment » or « de Gramont treatment ») provides an increase in clinical responses far greater than expected and higher than 5-FU/FA alone.

The schedules evaluated were :

**5-FU/FA + CPT-11 treatment schedule**

First schedule 5-FU/FA + CPT-11 (AIO treatment schedule) :
FA 500 mg/m² i.v. was administered over 2 hours followed by the administration of 5-FU (2300 mg/m²)* i.v. infusion over 24 hours, once a week for 6 weeks, which was followed by one week rest. (one cycle). For the same cycle, 80 mg/m$^2$ of CPT-11 was administered i.v. once a week. Each cycle was reproduced until a progression (stabilization or improvement in the disease) was observed.

Second schedule 5-FU/FA + CPT-11 (de Gramont treatment schedule)
On days 1 and 2 : FA 200 mg/m² i.v. was administered over 2 hours followed by the administration of 400 mg/m² 5-FU i.v. bolus and 600 mg/m² 5-FU i.v. over 22 hours (one cycle). The same doses and regimen were given every 2 weeks until a progression is observed. At the same time, 180 mg/m$^2$ CPT-11 was administered i.v. every 2 weeks until a progression was observed.

* (2300-2600 mg/m² can be used).

**5-FU/FA treatment schedule**

First schedule 5-FU/FA (AIO treatment schedule) :
FA 500 mg/m² i.v. was administered over 2 hours followed by the administration of 5-FU (2600 mg/m²) i.v. infusion over 24 hours, once a week for 6 weeks, which was followed by one week rest. (one cycle). Each cycle was reproduced until a progression was observed.

Second schedule 5-FU/FA (de Gramont treatment schedule)
On days 1 and 2 : FA 200 mg/m² i.v. was administered over 2 hours followed by the administration of 400 mg/m² 5-FU i.v. bolus and 600 mg/m² 5-FU i.v. over 22 hours

(one cycle). The same doses and regimen were given every 2 weeks until a progression was observed.

**Study objectives**

The primary objective of the study was evaluation of the response rate in patients with metastatic colorectal cancer previously untreated with chemotherapy for advanced disease. In addition to response rate, the sample size in the study allowed observation of a significant improvement of time to progression by 50 % (6 months versus 9 months).

Treatments were administered until disease progression occurred or unacceptable toxicity or withdrawal of consent.

In said study, at least 338 patients were considered as necessary to show a statistically significant difference in response rate between patients treated with 5-FU/FA alone and patients treated with CPT-11 in combination with the same schedule of 5-FU/FA, assuming a 35 % response rate versus 50% respectively.

**Selection criteria :**

The main inclusion and exclusion selection criteria were :
a histologically proven adenocarcinoma of the colon or rectum and at least one bi-dimensionally measurable lesion according to WHO (World Health Organization) criteria. ; WHO performance status ≤ 2 ; No prior chemotherapy other than (neo) adjuvant chemotherapy ended more than six months before randomisation was allowed.

**Study assessments :**

Physical examination, WHO performance status, hematology, and biochemistry had to be done before each infusion during the study treatment period. Radiological assessments to evaluate the antitumour response had to be performed following every cycle [6 weeks for every two weeks schedule (de Gramont schedule), 7 weeks for weekly schedule (AIO schedule)].

**Patient population :**

- Metastatic colorectal cancer patients, previously untreated with chemotherapy for advanced disease (prior adjuvant chemotherapy allowed if ended > 6 months before study entry) ;
- Measurable or evaluable disease ;
- Metastatic colorectal cancer patients who have documented progression after at least one 5-FU regimen for advanced disease ;
- Bi-dimensionnally measurable or evaluable lesion.

**Conclusion :**

The present phase III randomised trial has demonstrated the superiority of combining CPT-11 with the most active high dose infusional 5-FU/FA regimen over 5-FU/FA alone using the same infusional regimen. Both the weekly AIO regimen and the every two weeks de Gramont regimen have shown similar efficacy results with significantly higher response rates and longer time to progression over bolus 5-FU/FA (J. Clin. Oncol, 15 (2), 808-815 (1997) ; J. Clin. Oncol, 16(2), 418-426 (1998) ). Therefore using one or the other regimen, chosen by the participating centers according to their local habits, has been shown as the most valid option to establish the role of CPT-11 in combination with 5-FU/FA for the first line treatment of CRC in Europe.

The CPT-11 combination group used the same schedule of 5-FU/FA as in the control group.

This phase III randomized study also demonstrated the superiority of combining CPT-11 and 5-FU/FA infusional regimens over the same regimen of 5-FU/FA infusional alone in patients with MCRC previously untreated with palliative chemotherapy. A total of 387 patients were randomized : 199 on CPT-11 combination and 188 in the 5-FU/FA alone group. The patient population randomized into this study was representative of the usual patient population with MCRC suitable for CPT-11 containing chemotherapy.

In the per protocol population, a significantly higher response rate was observed with CPT-11 combination compared with 5-FU/FA alone : 40.8 % versus 23.1 % ($p<0.001$). Complete responses occurred only in the CPT-11 combination group in patients with visceral involvement or soft tissue lesions. In a stepwise multivariate

analysis, the odds for response in patients receiving CPT-11 combination was 2.6 times higher than on 5-FU/FA when adjusting for significant covariates (weight loss and time from diagnosis to first metastasis).

A significantly longer duration of response and stabilisation was also observed in favour of CPT-11 combination (8.6 months versus 6.2 months, p=0.0003).

Median time to progression (TTP) was also significantly longer with CPT-11 combination group : 6.7 months versus 4.4 months (p=0.0001). In a stepwise multivariate analysis, the risk for progression increased by 62% with 5-FU/FA alone after adjustment for significant covariates (age and liver involvement).

This trial demonstrates a survival advantage which was clinically relevant with a median of 16.8 months with CPT-11 combination versus 14.0 months with 5-FU/FA alone (p=0.028), and which is among the longest median survival ever published with combination chemotherapy in MCRC in a multicentric setting. This significant median survival advantage is obtained despite the fact that further chemotherapy (administered to around 50% of patients) might have lowered the overall survival benefit. Second line treatment was left to investigator's decision in the best interest of their patients. Of note, 31% of patients in the 5-FU/FA group received second line CPT-11 which has been demonstrated to be efficient and nevertheless the difference in survival was still significant, underlining the importance of introducing CPT-11 in first line treatment of patients with advanced colorectal cancer.

Both the weekly and every 2 weeks CPT-11 combinations were shown to be feasible at the dose and schedule initially planned. The median duration on study was slightly longer in the CPT-11 combination group compared with the 5-FU/FA alone group (24.0 versus 21.0 weeks in the weekly schedule and 24.6 versus 18.0 weeks in the every two weeks schedule, respectively). The number of cycles (7-week duration on the weekly schedule and 6-week duration on the every two weeks schedule) administered at the initial planned dose were comparable between the CPT-11 combination group and the 5-FU/FA group in each schedule (51.1% versus 50.6% on the weekly schedule and 84.6% versus 82.7% on the every 2 weeks schedule).

In summary, in this first phase III randomised trial using CPT-11 combination with 5-FU/FA, consistent significant advantage in terms of efficacy and clinical benefit i.e., response rate, median TTP, median TTF, median time to PS deterioration and median

survival and quality of life were shown in favour of the CPT-11 combination group. No other combination therapy had shown such a high antitumour efficacy over high dose infusional 5-FU/FA regimens at time of starting this phase III. More recently, oxaliplatin in combination with 5-FU/FA infusional did not achieve a significant advantage in median survival time, although it had achieved a higher response rate and longer TTP over 5-FU/FA infusional alone.

It is to be understood that in the above mentioned study, CPT-11 has been administered by i.v. route and could alternatively be administered by oral route. In such an alternative to an oral administration, CPT-11 would be administered p.o. for each schedule at the dose of 60 to 70 mg/m$^2$ every day during 5 consecutive days, with the same regimen reproduced every 3 weeks.

As of today, the CPT-11 combination is the only combination regimen in MCRC to demonstrate a survival advantage and a consistency in anti-tumour efficacy over high dose infusional 5-FU/FA. The median survival of 16.8 months achieved, with a trend to a better quality of life, using CPT-11 combination is a step forward in the management of patients with MCRC.

The superiority of the CPT-11 combination is achieved with an acceptable and manageable safety profile even though more toxicities occured compared with 5-FU/FA alone. The risks represented by neutropenia and its complications, as well as diarrhoea and mucositis are favourably counterbalanced by the high efficacy achieved with better quality of life on CPT-11 combination with 5-FU/FA infusional regimens.

Therefore CPT-11 in combination with 5-FU/FA infusional regimens should be considered as the treatment of choice in first line treatment of patients with advanced colorectal cancer.

## CLAIM

1 - A method of treating cancer, said method comprising administering to a patient in need of said treatment at least one camptothecin derivative and 5-FU in an amount and in a schedule of administration synergistically effective to treat said cancer.

# INTERNATIONAL SEARCH REPORT

Interr nal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/47 A61K31/505 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

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Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | L.SALTZ E.A.: "CPT-11 (irinotecan) and 5-fluorouracil: a promising combination for therapy of colorectal cancer" EUROPEAN JOURNAL OF CANCER, vol. 32A, no. 3, 1996, page 24-31 XP000939032 cited in the application page S24 page S30, column 1 | 1 |
| X | R.M.GOLDBERG, C.ERLICHMAN: "Irinotecan plus 5-FU and leucovorin in advanced colorectal cancer: North American trials" ONCOLOGY, vol. 12, no. 6, 1998, pages 59-63, XP000939051 page 59 page 60 | 1 |

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[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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|---|---|---|
| X | DATABASE EMBASE 'Online!<br>ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL;<br>1998320539, 1998<br>M.NISHIYAMA: "Irinotecan (CPT-11) in the treatment of gastrointestinal cancers"<br>XP002146556<br>abstract | 1 |
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| X | V.PAVILLARD E.A.: "Combination of irinotecan (CPT11) and 5-fluorouracil with an analysis of cellular determinantsof drug activity"<br>BIOCHEMICAL PHARMACOLOGY,<br>vol. 56, no. 10, 1998, pages 1315-1322,<br>XP000939083<br>page 1315<br>page 1319<br>page 1320<br>page 1321 | 1 |

1